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Chapter 9

GALLBLADDER MOTILITY IN CROHN'S DISEASE: Influence of disease localisation and bowel resection

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Gallbladder Motility in Crohn Disease: Influence of Disease Localization and Bowel Resection

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Background: Patients with Crohn disease (CD) have an increased risk of developing gallstones. Among other factors, gallbladder motility may have a role in the pathogenesis of gallstone formation. We have evaluated whether gallbladder motor function is affected in Crohn disease with special emphasis on the influence of disease localization and previous bowel resection. **Methods:** Thirty-seven patients (20 females and 17 males, age 36 ± 2 years) with inactive Crohn disease (CDAI < 150) were studied: 15 patients after ileocecal resection and 22 non-operated patients; 12 had small bowel disease and 10 had large bowel disease. Nineteen healthy subjects (10 female; 9 male, age 30 ± 2 years) served as controls. Gallbladder volumes were measured in the fasting state and at regular intervals for 2 h after ingestion of a solid meal (780 kcal). Blood samples were drawn at regular intervals for determination of cholecystokinin (CCK) and peptide YY (PYY). **Results:** Fasting gallbladder volumes were significantly ($P < 0.05$) reduced in patients with large bowel disease (20.8 ± 2.1 ml) or after ileocecal resection (18.3 ± 2.4 ml) compared to patients with small bowel disease (28.0 ± 2.1 ml) and controls (27.2 ± 1.8 ml). Fasting plasma CCK levels were significantly ($P < 0.05$) higher in patients with large bowel disease or after ileocecal resection compared to patients with small bowel disease and controls. Postprandial gallbladder emptying and endogenous plasma CCK and PYY secretion in patients with Crohn disease were not different from controls. **Conclusions:** Fasting gallbladder volume is decreased and fasting plasma CCK levels are increased in patients with Crohn disease of the large bowel and patients after ileocecal resection. Postprandial gallbladder motility, CCK and PYY release were not affected in patients with Crohn disease.

Key words: Gallbladder motility; Crohn disease; cholecystokinin; peptide YY

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Patients with Crohn disease have an increased risk of developing gallstones (1–5). Several studies have reported a gallstone prevalence of about 30% in patients with Crohn disease compared to 8% among age-matched healthy subjects (1–3). This reported prevalence is, however, not equally distributed among the group of patients with Crohn disease. Patients with Crohn disease confined to the ileum or after ileal resection have a higher prevalence of gallstones of around 34% while the prevalence is only 5% in patients with the disease confined to the colon (1, 2).

Pathophysiological factors underlying cholesterol gallstone disease in general are: excess biliary cholesterol secretion resulting in cholesterol supersaturation; increase in nucleation-promoting factors; and alterations in gallbladder motility (6, 7). In patients with Crohn disease, disturbances in the enterohepatic circulation of bile salts owing to disease or resection of the ileum resulting in bile salt malabsorption and increased biliary cholesterol have been proposed as the most important mechanism (8, 9). The role of gallbladder motility in the pathogenesis of gallstone formation in Crohn disease is less clear because the published data are conflicting (10–13). In three studies, impaired postprandial gallbladder contraction in patients with Crohn disease was reported while no evidence for abnormal gallbladder emptying was found in other studies (10–13). The aim of the present study was, therefore, to evaluate fasting and meal-stimulated gallbladder motility in a large group of Crohn disease patients with different disease localization and with or without ileocecal resection. As the gallbladder motor response to a meal is mainly controlled by various gut hormones released during the intestinal phase, basal and meal-stimulated plasma concentrations of proximal and distal gut hormones were also measured.

Subjects and Methods

Subjects

Thirty-seven patients with inactive Crohn disease (Crohn disease activity index (CDAI) median 63; range, 15–149) were included. Patients with concomitant diseases such as diabetes mellitus and hypertension were excluded from the study. None of the patients had clinical symptoms or ultrasonographical evidence of gallstones. Fifteen of the 37 patients had previously undergone ileocecal resection (median 6 years; range, 2–10 years). The mean length of the resected ileocecal segment was 42 ± 10 cm. Twelve of the remaining 22 patients had small bowel disease and 10 had colonic disease. At the time of the experiment 26 patients were on medication among which 6 patients were on prednisone, 9 on 5-ASA derivatives and 11 on both prednisone and 5-ASA derivatives. Nine of the female patients used oral contraceptives. All medications were continued except on the morning of the experiment. Further clinical characteristics of the three patient groups are presented in Table I.

Nineteen healthy subjects without any history of gastrointestinal disease or abdominal surgery served as controls (Table I). The use of oral contraceptives was reported in 7 of the 9 female healthy subjects. Studies were performed irrespective of the time of the menstrual cycle. The study protocol had been approved by the ethics committee of the Leiden University Medical Center.

Study protocol

All subjects were studied at 0830 h after an overnight fast. After two measurements of basal gallbladder volume an intravenous cannula was inserted into the antecubital vein of one arm for blood sampling. A solid meal consisting of 50 g fat, 42 g protein and 38 g carbohydrates (780 kcal) was ingested at time $t = 0$ min. Gallbladder volumes were measured and blood samples for determination of gut hormones cholecystokinin (CCK), pancreatic polypeptide (PP) and peptide YY (PYY) were drawn at $t = -15$, 0, 10, 20, 30, 45, 60, 75, 90, 105 and 120 min after meal ingestion.

Gallbladder volume

Gallbladder volumes measured by real-time ultrasonography (Toshiba, 3.5 MHz transducer) were calculated by the sum of cylinders method using a computerized system (14, 15). In this method the longitudinal image of the gallbladder is divided into series of equal height, with diameter perpendicular to the longitudinal axis of the gallbladder image. The uncorrected volume is the sum of volumes of these separate cylinders. To correct for the displacement of the longitudinal image of the gallbladder from the central axis, a correction factor is calculated from the longitudinal and transversal scans of the gallbladder. Gallbladder volume is calculated by multiplication of the uncorrected volume with the square of the correction factor. The mean of two measurements was used for analysis. The assumptions and the mathematical formula used to calculate gallbladder volume have been described and validated previously (14, 15).

Hormone assays

Blood samples for measurement of plasma pancreatic polypeptide (PP), cholecystokinin (CCK) and peptide YY (PYY) were drawn at time $t = -15$, 0, 15, 30, 45, 60, 90, 120, 150 and 180 min during each experiment. The blood samples were collected in EDTA containing ice-chilled tubes. The samples were centrifugated at a rate of 3000 rpm for 10 min at a temperature of 4 °C. Plasma CCK was measured by a sensitive and specific radioimmunoassay (16). This antibody binds to all CCK peptides including sulphated CCK octapeptide, but not gastrin. The detection limit of the assay is 0.3 pM plasma. Plasma PYY was measured by radioimmunoassay. PYY antiserum was generated in rabbits by intracutaneous injections of synthetic human PYY (BACHEM A.G., Switzerland). PYY was labelled with ^{125}I using chloramine T. There is no cross-reactivity with PP or VIP. The detection limit is 10 pM plasma. Both PYY (1–3) and PYY (3–36) bind to the antibody in dilutions up to 25,000. Plasma PP was determined by radioimmunoassay as described previously (17).

Data and statistical analysis

Data are expressed as mean ± standard error of the mean. Postprandial gallbladder emptying was calculated as the percentage of the basal volume. Integrated incremental values for plasma hormone secretion were calculated as the area under the plasma concentration curve after subtraction of the basal value at $t = 0$. Multiple analysis of variance (MANO-

Table I. Characteristics of the three patient groups and of the healthy controls. Disease duration and CDAI are expressed as medians and ranges; age and body mass index are expressed as mean ± standard error of the mean

	Controls ($N = 19$)	Ileal CD ($N = 12$)	Colonic CD ($N = 10$)	Ileocecal resection ($N = 15$)
Age (years)	30 ± 2	34 ± 4	40 ± 4	37 ± 4
Sex (F/M)	9/10	5/7	7/3	6/9
Body mass index (kg/m^2)	23 ± 1	22 ± 3	24 ± 3	23 ± 2
Disease duration (years)	—	6 (2–23)	7 (3–22)	6 (2–25)
CDAI	—	76 (9–149)	90 (18–134)	80 (12–139)

Table II. Fasting and residual gallbladder volumes and maximal percentage of postprandial gallbladder emptying in the three patient groups and healthy controls. Data are expressed as mean ± standard error of the mean

	Controls ($N = 19$)	Ileal CD ($N = 12$)	Colonic CD ($N = 10$)	Ileocecal resection ($N = 15$)
Fasting volume (ml)	27.2 ± 1.8	28.0 ± 3.3	20.8 ± 2.1*	18.3 ± 2.4*
Residual volume (ml)	8.0 ± 0.9	9.6 ± 2.8	7.0 ± 1.3	6.0 ± 1.0
Maximal emptying (%)	70 ± 4	66 ± 8	67 ± 4	68 ± 3

* $P < 0.05$ compared to patients with ileal Crohn disease (CD) and controls.

VA) was used to compare gallbladder volume, plasma PP and CCK levels between and within groups and to analyse the influence of age, gender and the use of medication on gallbladder volume. Coefficient of linear correlation (Spearman) was used to calculate the correlations between fasting gallbladder volumes and the length of the resected segment and CDAI. The level of significance was set at $P < 0.05$.

Results

Fasting gallbladder volume

Mean basal gallbladder volume was significantly ($P < 0.05$) smaller in patients with large bowel disease and after ileocecal resection compared to patients with small bowel disease and to controls (Table II). Individual data of fasting gallbladder volumes are shown in Fig. 1. No correlation was found between fasting gallbladder volume and CDAI ($r = 0.16$; $P = 0.2$) or length of the resected segment ($r = 0.048$; $P = 0.7$).

Postprandial gallbladder emptying

After meal ingestion, gallbladder volume decreased significantly ($P < 0.01$) in all Crohn disease patients and healthy controls (Fig. 2). The degree of postprandial gallbladder emptying was not significantly different between the patient groups and controls. Residual gallbladder volumes and maximal postprandial gallbladder emptying for all groups are given in Table II.

Plasma PP

Basal plasma PP levels were not significantly different between the four groups (Table III). Plasma PP levels significantly increased ($P < 0.001$) in response to the meal in all patients and control subjects. Postprandial integrated plasma PP concentration was not significantly different between the groups (Table III).

Plasma CCK

Basal plasma CCK levels were significantly ($P < 0.05$) higher in patients with large bowel Crohn disease and after ileocecal resection compared to patients with small bowel disease and controls (Table III). Plasma CCK levels significantly ($P < 0.01$) increased in response to the meal in all four groups (Fig. 3). Postprandial-integrated plasma CCK concentrations were not significantly different between patients and controls (Table III).

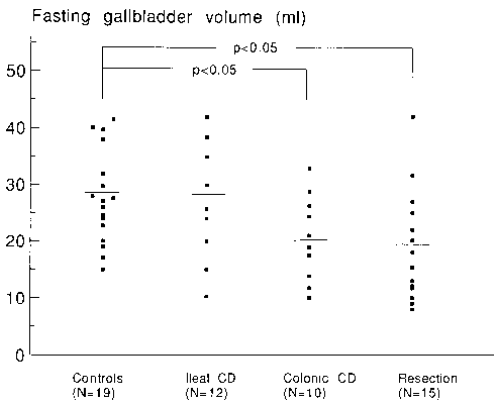

Fig. 1. Individual data of fasting gallbladder volume (ml; mean ± standard error of the mean) in patients with Crohn disease of the ileum and colon, patients after ileocecal resection and healthy controls.

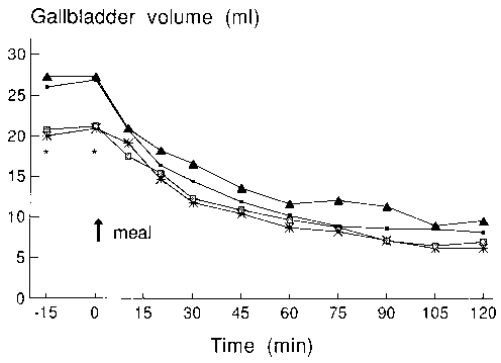

Fig. 2. Gallbladder volume (ml; mean ± standard error of the mean) during fasting and after meal ingestion in patients with Crohn disease of the ileum (closed triangles), of the colon (big squares), in patients after ileocecal resection (crosses) and healthy controls (small squares). * $P < 0.05$ compared to patients with ileal Crohn disease and controls.

Table III. Basal and postprandial integrated plasma concentrations of PP, CCK and PYY in patients with small and large bowel Crohn disease, patients after ileocecal resection and healthy controls

	Controls ($N = 19$)	Ileal CD ($N = 12$)	Colonic CD ($N = 10$)	Ileocecal resection ($N = 15$)
Fasting PP (pM)	49 ± 3	52 ± 6	41 ± 9	43 ± 8
Fasting CCK (pM)	0.7 ± 0.2	0.8 ± 0.1	1.6 ± 0.3*	1.5 ± 0.2*
Fasting PYY (pM)	19 ± 1	21 ± 3	15 ± 1	21 ± 1
AUC PP (pM*120 min)	8908 ± 1597	7732 ± 1190	7697 ± 1203	7929 ± 717
AUC CCK (pM*120 min)	137 ± 15	145 ± 46	217 ± 33	204 ± 40
AUC PYY (pM*120 min)	406 ± 120	515 ± 200	514 ± 133	400 ± 107

* $P < 0.05$ compared to patients with ileal Crohn disease and to controls.

Plasma PYY

Basal plasma PYY levels were not significantly different between Crohn disease patients and control subjects (Table III). A significant ($P < 0.05$) rise in plasma levels of PYY was found in the last 30 min after meal ingestion ($t = 90$, 105 and 120 min) in all the patient groups and in the healthy controls. Postprandial-integrated plasma PYY concentrations were not significantly different between the four groups (Table III).

Discussion

The results of the present study show that fasting gallbladder volume is significantly smaller in patients with Crohn disease of the large bowel and in patients after ileocecal resection compared to patients with small bowel disease and to controls. On the other hand, gallbladder emptying in response to a meal is not significantly different between the patients and the controls. We have included in this study only patients with inactive Crohn disease and without evidence of cholesterol gallstones. Patients who had developed cholesterol gallstones were excluded since it has been documented that cholesterol gallstones affect gallbladder motility (18).

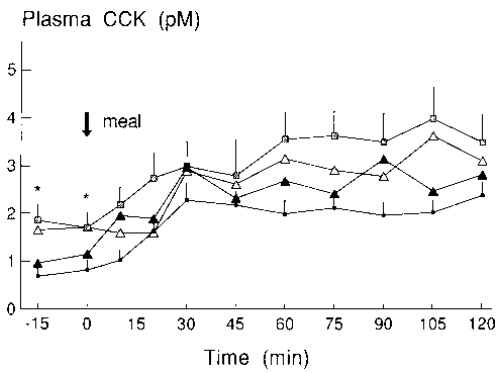

Fig. 3. Basal and postprandial plasma CCK levels (pM; mean ± standard error of the mean) in patients with Crohn disease of the ileum (closed triangles), of the colon (big squares), in patients after ileocecal resection (open triangles) and healthy controls (small squares). * $P < 0.05$ compared to patients with ileal Crohn disease and controls.

Fasting gallbladder tone and volume are controlled by both hormonal and neural pathways. Alterations in one of these factors may affect gallbladder motility. Indeed, plasma CCK levels were significantly higher in patients with large bowel disease or after ileocecal resection compared to patients with small bowel disease and to controls. CCK is released from the upper small bowel and is the most important hormonal mediator of gallbladder motility (19). CCK is not only involved in postprandial gallbladder motility but also plays an important role in regulating basal gallbladder volume. In humans, administration of the CCK antagonist loxiglumide significantly increases gallbladder volume (20). The elevated fasting plasma CCK levels in patients with large bowel disease and after ileocecal resection correlate with small fasting gallbladder volume found in these groups. This finding is in agreement with a previous study by Salemans et al. (21) who found that basal plasma CCK is increased and fasting gallbladder volume is decreased in patients after protocolectomy with ileal pouch anal anastomosis, suggesting a role for the colon in controlling plasma CCK release from the proximal gut.

Gastrointestinal peptides are released also from the distal small bowel and large bowel. Peptide YY (PYY) is such a distal gut hormone. It is a mediator of the so-called ileal and colonic brake–a negative feedback from the distal to the proximal gastrointestinal tract (22, 23). The highest concentrations of PYY-producing cells are found in the ileum, colon and rectum (23). It has been shown in dogs that PYY infusion induces gallbladder relaxation after CCK-stimulated gallbladder contraction (24). In the present study fasting plasma PYY levels were not significantly different between patients with large bowel disease or after ileocecal resection compared to patients with small bowel disease and to controls, suggesting that PYY does not account for the differences in fasting gallbladder volume found between these patient groups.

The vagus nerve is an important cholinergic neural mediator of fasting gallbladder motor activity (25). In both humans and dogs, gallbladder volume is increased after truncal vagotomy or during cholinergic blockage with atropine while it is decreased during administration of the vagal cholinergic stimulus bethanechol (26, 27). Lindgren et al. have shown that autonomic nerve dysfunction is frequently

present in patients with Crohn disease especially vagus dysfunction (28). Based on the results of these studies theoretically, the gallbladder volume should be increased in patients with Crohn disease compared to controls. However, the finding of a smaller fasting gallbladder volume in patients with large bowel disease and after ileocecal resection does not support the hypothesis of autonomic dysfunction as a factor accounting for the smaller fasting gallbladder volume.

In contrast to fasting gallbladder volume, no significant difference was found in postprandial gallbladder emptying between patients with colonic disease or after ileocecal resection compared to patients with small bowel disease and controls. Although several studies on postprandial gallbladder emptying in patients with Crohn disease have been performed, no consistent results have been obtained (10–13). Murray et al. documented that gallbladder emptying in response to a fatty meal is impaired in patients with Crohn disease. The most pronounced impairment has been observed in patients with both large and small bowel disease or after a previous resection (10). Consistent with the results of Murray et al., Damiao et al. have shown that gallbladder emptying in response to a solid meal is significantly reduced in patients with Crohn disease, an abnormality which is not influenced by gastric emptying (13). Unfortunately, differences in gallbladder emptying related to the localization of the disease or after resection were not analysed in the latter study. On the other hand, Maurer et al. found no evidence for abnormal postprandial gallbladder emptying in a group of 17 Crohn disease patients with small and/or large bowel disease or after previous resection (12). The discrepancy in results between these studies could be related to differences in the composition of the test meals and differences in patient population. It has previously been shown that the pattern and magnitude of postprandial gallbladder emptying are determined by the type, composition and caloric value of the meal (29). Differences in patient population due to the heterogeneous nature of Crohn disease with respect to disease duration and localization, bowel resection and the use of medication are probably the most important factors contributing to the different results found between the studies. In the present study, we have measured gallbladder volume in patients with inactive Crohn disease and data were analysed according to disease localization and bowel resection.

Since no differences were found in postprandial gallbladder emptying and residual volume, questions must be raised concerning the role of gallbladder motility in the formation of gallstones in patients with Crohn disease. Residual volume and fractional emptying have been documented to be the most important factors promoting stasis and gallstone formation (30). It is not known whether smaller fasting gallbladder volumes are relevant for gallstone formation. Instead, there is evidence suggesting that patients with cholesterol gallstones are characterized by enlarged fasting gallbladder volumes (31). Given the higher prevalence of gallstones in patient with Crohn ileitis or after ileocecal resection, it is obvious that other pathogenetic factor(s) for gallstone formation must be involved. Excess of biliary cholesterol in relation to phospholipids and bile acids due to bile acid malabsorption in patients with Crohn disease in the ileum or after ileocecal resection has been reported (8, 9). However, recent studies have documented that cholesterol saturation of bile is not increased in patients with Crohn disease after ileocecal resection (32, 33). Not only the size but also the composition of the bile acid pool is relevant for cholesterol gallstone formation. The secondary bile acid deoxycholic acid stimulates cholesterol secretion to a larger extent than primary bile acids (34). The biliary concentration of deoxycholic acid is decreased in patients with Crohn colitis who have a low incidence of gallstones (35, 36). Data on the concentration of deoxycholic acid in patients with Crohn disease of the ileum or after ileocecal resection are less consistent (32, 36, 37). Lapidus & Einarsson have found that in addition to the decreased concentration of deoxycholic acid in duodenal bile, the amount of ursodeoxycholic acid is increased in patients after ileocecal resection (32). It is also possible that pigment rather than cholesterol gallstones are present in patients with ileal dysfunction or after ileal resection. It has been shown in animal models that after ileal resection especially pigment gallstones are formed (38). More recently, Brink et al. have shown that gallbladder bile of patients with ileal Crohn disease is saturated with unconjugated bilirubin (39).

In conclusion, patients with inactive Crohn disease of the large bowel and patients after ileocecal resection have smaller fasting gallbladder volumes and increased basal plasma CCK levels. Gallbladder motility and subsequent hormone release in response to a meal are, on the other hand, not affected in patients with inactive Crohn disease irrespective of disease localization and previous bowel resection. Gallbladder (dys)motility does not seem to contribute to gallstone formation in patients with Crohn disease.

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